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Simvastatin as a neuroprotective treatment for m

Submission date
19/11/2015

Recruitment status
No longer recruiting

Registration date
19/11/2015

Overall study status
Completed

Last Edited
21/12/2023

Condition category
Nervous System Diseases

[X] Prospectively registered

[X] Protocol

[X] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims

Parkinson's disease (PD) is a long-term medical condition which is caused by the gradual loss of nerve cells (neurons) in a part of the brain called the substantia nigra. These neurons are normally responsible for producing dopamine, a chemical messenger (neurotransmitter) which carries signals around the brain that help to coordinate movement. In people suffering from PD, these neurons gradually die over time, causing the level of dopamine in the brain to gradually fall. As the levels of dopamine become lower, the brain is unable to coordinate movement as effectively, causing abnormal movements such as stiffness, tremor (uncontrollable shaking) and slowness of movement (bradykinesia). Currently, PD affects more than 127,000 people in the UK alone, with a further 10,000 diagnosed each year. Unfortunately, there is no cure for PD and so current therapies are only able to help relieve the symptoms, such as by artificially replacing dopamine or preventing the body from breaking it down. These treatments ultimately fail however, as they are unable to prevent the overall loss of neurons in the brain. Neuroprotection is an area of research which aims to protect nerves from damage. Studies have shown that statins (a group of medications which lower cholesterol) are potentially neuroprotective. The way this works is still only partly understood however, and so more research is needed to find out if statins have the potential of being neuroprotective. The aim of this study is to find out whether simvastatin has potential as a neuroprotective therapy in PD.

Who can participate?

Adults aged between 40 and 90 years old who have been diagnosed with idiopathic PD (i.e. the cause is unknown), with no current or previous use of statins.

What does the study involve?

Participants are randomly allocated to one of two treatment groups. In one group, participants are given capsules of simvastatin to take orally (by mouth) for 24 months. In the other group, participants are given placebo (dummy) capsules to take orally for 24 months. At the start of the study, when they receive their medication, participants complete a number of questionnaires and motor (movement) tests (a walking test and a finger tapping test). Participants in both groups also attend a further 6 clinic visits after 1, 6, 12, 18 and 24 months, where they are asked about their health and any medication they are taking, as well as repeating the questionnaires and motor tests. For 4 of these clinic visits, the participants will be asked to attend in the 'OFF medication' state (having omitted their usual PD medication) so that the researchers can get a true picture of their disease without it being masked by their normal medication.

What are the possible benefits and risks of participating?
Participants may or may not benefit directly from taking part in the study, but by taking part they will be contributing to a study which could potentially bring future benefit to large numbers of people with PD. There are no significant risks of taking part, however participants may experience side effects from the medication (such as muscle aches and pains) and could experience pain or bruising from blood testing.

Where is the study run from?
24 NHS hospitals in England (UK)

When is the study starting and how long is it expected to run for?
January 2015 to September 2020

Who is funding the study?
1. Cure Parkinson's Trust (UK)
2. The JP Moulton Charitable Foundation (UK)

Who is the main contact?
Mr Doug Webb

Study website
https://penctu.psmd.plymouth.ac.uk/pdstat/

Contact information

Type(s)
Public

Contact name
Mr Doug Webb

Contact details
Peninsula Clinical Trials Unit
Plymouth University Peninsula Schools of Medicine and Dentistry
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Plymouth Science Park
Plymouth
United Kingdom
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Additional identifiers

EudraCT/CTIS number
2015-000148-40

IRAS number

ClinicalTrials.gov number
NCT02787590

Secondary identifying numbers
CPMS 19666

Study information

Scientific Title
Simvastatin as a neuroprotective treatment for Parkinson's disease: a double--blind, randomised, placebo-controlled futility study in patients of moderate severity

Acronym
PD STAT

Study objectives
The aim of this study is to establish whether the cholesterol-lowering drug, simvastatin, has potential as a neuroprotective therapy in Parkinson's disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Newcastle and North Tyneside 2 Research Ethics Committee, 12/10/2015, ref: 15/NE/0324

Study design
Double-blind placebo-controlled multi-centre randomized futility study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Topic: Dementias and neurodegeneration; Subtopic: Parkinson’s Disease; Disease: Parkinson's disease

Interventions
Participants in this study will be randomly allocated to one of two treatment groups in a 1:1 ratio:
Intervention group: Participants will receive oral simvastatin capsules to take daily for 24

months.
Control group: Participants will receive oral matched-placebo capsules to take daily for 24 months.

Trial treatment will be provided to the participants at the baseline, 1 month, 6 month, 12 month and 18 month clinic visits; the maximum supply provided will be a 6 month supply. Bottles containing 100 capsules of either 40mg simvastatin or matched placebo will be issued to the participants.

Over a 26 month period, participants in both treatment groups will attend scheduled study clinic visits, complete a number of validated assessments and receive telephone contacts.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Simvastatin

Primary outcome measure
Patient motor skills are determined using the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part III) in the OFF state at 12 and 24 months.

Secondary outcome measures
1. The overall impact of PD on the participant is assessed using the MDS-UPDRS total score in the practically defined ON state at 12 and 24 months
2. The impact of PD on activities of daily living is assessed using the MDS-UPDRS part II subscale score in the practically defined ON state at 12 and 24 months
3. Motor skills are assessed using timed motor tests (finger tapping and timed walk test (10MWT)) in the OFF state at 12 and 24 months
4. Depression is assessed using the Montgomery and Asberg Depression Rating Scale (MADRS) at 12 and 24 months
5. Cognition is assessed using the Addenbrooke’s Cognitive Assessment-III (ACE-III) at 12 and 24 months
6. The presence of the non-motor features of PD is captured using the Non-Motor Symptom assessment scale (NMSS) at 12 and 24 months
7. A PD-specific health status is assessed using the Parkinson’s disease Questionnaire (PDQ-39) at 12 and 24 months
8. Changes in PD medication are measured by capturing a levodopa-equivalent dose (LED) at 12 and 24 months
9. Cholesterol levels are captured using total, HDL, LDL, and total/HDL ratio results at 12 and 24 months
10. The presence of PD-specific pain is captured using the King’s PD pain scale (KPPS) at 12 and 24 months
11. A current overall health status is captured using the EuroQoL 5D-5L (EQ-5D-5L) health status questionnaire at 12 and 24 months
12. The safety and tolerability of trial medication is assessed by adverse events (AEs) review at

12 and 24 months
13. The incidence of diabetes mellitus is assessed at 24 months using a glycated haemoglobin (HbA1c) level of 6.5% (48mmol/mol) as diagnostic of diabetes mellitus (WHO 2011)

Overall study start date
01/01/2015

Completion date
30/09/2020

Eligibility

Key inclusion criteria
1. Diagnosis of idiopathic PD
2. Modified Hoehn and Yahr stage ≤ 3.0 in the ON medication state
3. Age 40-90 years
4. On dopaminergic treatment with wearing-off phenomenon
5. Able to comply with study protocol and willing to attend necessary study visits

Participant type(s)
Patient

Age group
Adult

Lower age limit
40 Years

Upper age limit
90 Years

Sex
Both

Target number of participants
Planned Sample Size: 198; UK Sample Size: 198

Total final enrolment
235

Key exclusion criteria
1. Diagnosis or suspicion of other cause for parkinsonism
2. Known abnormality on CT or MRI brain imaging considered to be causing symptoms or signs of neurological dysfunction, or considered likely to compromise compliance with study protocol
3. Concurrent dementia defined by MoCA score <21
4. Concurrent severe depression defined by MADRS score >31
5. Prior intracerebral surgical intervention for PD including deep brain stimulation, lesional surgery, growth factor administration, gene therapy or cell transplantation
6. Already actively participating in a research study that might conflict with this trial
7. Prior or current use of statins as a lipid lowering therapy

8. Intolerance to statins
9. Untreated hypothyroidism
10. End stage renal disease (creatinine clearance <30 mL/min) or history of severe cardiac disease (angina, myocardial infarction or cardiac surgery in preceding two years)
11. eGFR <30 mL/min
12. History of alcoholism or liver impairment
13. Creatine kinase (CK) >1.1 x upper limit of normal (ULN)
14. Aspartate transaminase (AST) or alanine transaminase (ALT) >1.1 x ULN
15. Females who are pregnant or breast feeding or of child-bearing potential and unwilling to use appropriate contraception methods whilst on trial treatment
16. Currently taking any medication contraindicated with simvastatin use
17. Any requirement for statin use
18. Regular participation in endurance or high -impact sports
19. Unable to abstain from consumption of grapefruit -based products

Date of first enrolment
01/12/2015

Date of final enrolment
31/03/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Cornwall Hospital
2 Penventinnie Lane
Treliske
Cornwall
United Kingdom
TR1 3LQ

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

Study participating centre

Musgrove Park Hospital
Parkfield Drive
Taunton
United Kingdom
TA1 5DA

Study participating centre
Yeovil District Hospital
Higher Kingston
Yeovil
United Kingdom
BA21 4AT

Study participating centre
Christchurch Hospital
Fairmile Road
Christchurch
United Kingdom
BH23 2JX

Study participating centre
Royal United Hospital Bath
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
St Peter's Hospital
Guildford Road
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Queen's Hospital
Rom Valley Way
Romford
United Kingdom
RM7 0AG

Study participating centre
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Luton and Dunstable University Hospital
The L&D Hospital NHS Foundation Trust
Lewsey Road
Luton
United Kingdom
LU4 0DZ

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Salford Royal Hospital
Stott Lane

Salford
United Kingdom
M6 8HD

Study participating centre
Fairfield General Hospital
Rochdale Old Road
Bury
United Kingdom
BL9 7TD

Study participating centre
Royal Preston Hospital
Sharoe Green Lane North
Preston
United Kingdom
PR2 9HT

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Clinical Ageing Research Unit
Campus for Ageing and Vitality
Newcastle upon Tyne
United Kingdom
NE4 5PL

Study participating centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
King's College Hospital
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
United Kingdom
NR4 7UY

Study participating centre
Rotherham General Hospital
Moorgate Road
Rotherham
United Kingdom
S60 2UD

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Sponsor information

Organisation

Plymouth Hospitals NHS Trust

Sponsor details
Research Office
Level 2
MSCP
Bircham Park Offices
Morlaix Drive
Plymouth
England
United Kingdom
PL6 8BQ

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05x3jck08

Funder(s)

Funder type
Charity

Funder Name
Cure Parkinson's Trust

Funder Name
The JP Moulton Charitable Foundation

Results and Publications

Publication and dissemination plan
The study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the trial. Results of the study may also be presented at meetings of PD support groups or to other relevant lay audiences. The study results will be submitted for publication in international, high impact, peer-reviewed journals relating to neurology and PD. The study findings will be presented at regional, national and international meetings as appropriate.

Intention to publish date
30/06/2022

Individual participant data (IPD) sharing plan

The researchers intend to deposit anonymised patient-level data in the Critical Path for Parkinson's Consortium.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	07/10/2019	23/07/2020	Yes	No
Statistical Analysis Plan		24/08/2020	07/01/2022	No	No
Basic results		03/06/2021	16/06/2022	No	No
Results article		31/10/2022	01/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Protocol (other)		31/10/2022	21/12/2023	No	No
Statistical Analysis Plan		31/10/2022	21/12/2023	No	No